

Decision Memo for Positron Emission Tomography (FDG) for Myocardial Viability (CAG-00098N)

Decision Summary

CMS intends to revise the NCD at CIM 50-36 to state that (1) both SPECT or FDG PET are reasonable and necessary as a primary or initial diagnostic study for determining myocardial viability prior to revascularization; (2) PET continues to be reasonable and necessary following an inconclusive SPECT; (3) the greater specificity of PET makes using SPECT following an inconclusive PET of no added value and thus not reasonable and necessary.

[Back to Top](#)

Decision Memo

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Subject: PET for Myocardial Viability

Date: February 20, 2002

This memo serves four purposes: (1) briefly outlines the use of single photon emission computed tomography (SPECT) and positron emission tomography (PET) to assess ischemic cardiomyopathy and left ventricular dysfunction; (2) reviews the history of Medicare's coverage process on the use of PET for myocardial viability and provides a timeline of recent activities; (3) presents and analyzes the relevant scientific literature comparing PET to SPECT for the detection of myocardial viability; (4) announces our intention to issue an NCD revising CIM 50-36 and delineates the reasons for making a positive coverage decision for the use of PET as a primary or initial diagnostic study for determining myocardial viability and noncoverage of SPECT after PET.

Clinical Background

Cardiovascular disease (CVD) is a broad term encompassing several conditions, such as hypertension, coronary heart disease (CHD), congestive heart failure (CHF), and stroke. CVD is the number one cause of death in the United States, claiming 949,619 lives in 1998.¹ Of that total, 459,841 deaths were attributable to CHD. Eighty-five percent of the people who die of CHD are age 65 or older and, thus, Medicare beneficiaries.² In 1997, Medicare expenditures for the care of beneficiaries with CHD totaled \$10.8 billion.

The incidence of CHF in Medicare beneficiaries approaches 10 per 1000. Patients with this disease are at risk for increased morbidity and mortality. The mortality of this subset of patients correlates with the severity of left ventricular dysfunction. Annual mortality in patients with LVEF 31%-35% is approximately 9%, with LVEF 26%-30% is 12%, and with LVEF less than 25% is 24%. In addition to being treated medically, patients with coronary artery disease and reduced left ventricular function may receive surgical intervention that includes cardiac transplantation and myocardial revascularization. ³

Each of these alternatives entail mortality and morbidity risks of their own. In particular, the challenge of determining which group of patients will benefit from coronary artery bypass graft (CABG) through improved left ventricular function is dependent on the ability of revascularized myocardium to regain contractile function.

Myocardial metabolic imaging is a tool used to optimize the selection of patients for revascularization, and, potentially, the reversal of LV dysfunction with improved patient outcomes.

Several tests are available to clinicians to predict which patient will benefit from revascularization. Presently, SPECT imaging using Thallium 201 (TI 201) is widely used. It operates on the principle that TI 201 is distributed by coronary blood flow and is a marker of the degree of blood flow. It is extracted from the coronary circulation by viable myocardial cells and enables the clinician to determine the presence of ischemic cardiac areas following exercise. It is also used at rest to assess viability.⁴ The higher the regional uptake of thallium the more likely the region is viable. Fifty-percent thallium uptake relative to normal regions is a clinically useful threshold used to discriminate between nonviable and viable myocardium.

PET using F-fluorodeoxyglucose (FDG) as a tracer to study glucose metabolism in the heart and other organs is advocated by an increasing number of clinicians. FDG PET imaging is used to measure myocardial cell metabolism. An area of ischemic viable myocardial wall will show a mismatch between the blood flow and metabolism as measured by the tracer. Regions showing deficits in both perfusion and FDG uptake can be considered dead regions (scar). Conversely, an area showing a defect in blood flow but with preserved FDG uptake is said to show a blood flow-metabolism mismatch, and is considered still viable for revascularization. Additional radioactive tracers, such as 13-ammonia, are being studied for both perfusion and viability measures, but will not be addressed in this decision.

History of Medicare's Coverage on FDG PET for Myocardial Viability and Timeline of Recent Activities

On December 15, 2000, CMS (then known as the Health Care Financing Administration) published a decision memorandum on a request for broad coverage (CAG-00065) for all oncological indications, heart disease, and neurological disorders. The December 15th decision memorandum stated that HCFA had insufficient evidence to support coverage for the indication of myocardial viability except for the decision to cover the service following an inconclusive SPECT. The December 15th coverage decision reflected the findings of a Commonwealth Australian Technology Assessment (2000), which found FDG PET provided marginally more accurate information compared to SPECT in the assessment of myocardial viability. The technology assessment found slightly stronger evidence to support the coverage of PET as a sequential diagnostic imaging test following an inconclusive SPECT result. After the December 15th decision, it was suggested that this issue be reviewed for possible expansion of the coverage decision and be potentially referred to MCAC for review of possible additional uses of FDG PET for myocardial viability.

CMS requested an expedited review of the literature from AHRQ on July 20, 2001. The technology assessment's goal was to determine whether sufficient evidence exists to justify expansion of coverage of FDG PET for myocardial viability as a diagnostic tool and to provide background information on how it would influence treatment NCDs of cardiologists and surgeons.

On October 2, 2001, CMS received a letter from The American College of Cardiology (ACC) and the American Society of Nuclear Cardiology (ASNC) strongly urging Medicare reimbursement for cardiac Positron Emission Tomography (PET).

On October 2, 2001, CMS staff elected to:

1. Discontinue the full expedited review of the literature based upon preliminary conversations with AHRQ and discovery of two additional technology assessments - the Alberta Heritage Foundation for Medical Research (1999) and an International Network of Agencies for Health Technology Assessment (INHATA) (1999) summary of 11 technology assessments.
2. Not refer issue to MCAC panel, as originally stated in December 15th decision, since this topic is sufficiently addressed in the literature.
3. Continue the review of the literature by answering the question of how PET compares to SPECT in the assessment of myocardial viability.

On October 17, 2001, CMS received official letter from AHRQ summarizing their findings from the above mentioned technology assessments.

FDA Status

The FDA has determined that FDG "can be safe and effective in PET imaging in patients with CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function..."⁵

Summary of Evidence

In reviewing the December 15th coverage decision, CMS decided that the focus of the additional review of the literature would be limited to the effectiveness of FDG PET compared to SPECT thallium for the assessment of myocardial viability. Evidence reviewed by CMS included 3 technology assessments, AHRQ's summary of these TAs, additional published articles, and a position paper submitted by the American College of Cardiology (ACC) and the American Society of Nuclear Cardiology (ASNC).

Technology Assessments

Australian Department of Health and Aged Care

The Australian Department of Health and Aged Care published a technology assessment in August 2000 entitled *Report of the Commonwealth Review of Positron Emission Tomography*. One section addressed the "role of PET in the assessment for possible coronary revascularization of patients with CHD and impaired ventricular function." Specifically, it asked "whether PET adds any further valuable information to what would be known from previous investigations, and in particular, whether there is any added value in patients who have had SPECT". The articles included for their review fulfilled the following requirements:

- The study participants considered for revascularization either had both SPECT and PET, or the study participants had negative SPECT results. Studies that randomized participants to either SPECT or PET were also included.
- The studies explored which patients, based on their test results, have more positive outcomes following revascularization.

The assessment identified 159 eligible studies. Of those, 126 abstracts and 33 full papers were reviewed. The technology assessment only reviewed one study that was correctly designed to compare the incremental value of PET over SPECT⁶. Of patients with differing test results, PET was a better predictor of myocardial recovery compared to SPECT. Two additional studies suggested that PET is likely to have a higher specificity than SPECT⁷. All studies reviewed were observational and provided only indirect evidence as to patient morbidity and mortality.

Alberta Heritage Foundation for Medical Research (October 1999)

The Alberta Heritage Foundation for Medical Research prepared a technology assessment entitled *Functional Diagnostic Imaging in the Assessment of Myocardial Viability* (1999) in response to continued interest in positron emission tomography and other functional diagnostic imaging methods found within the Alberta health care system. Comparisons to PET included SPECT using thallium - 201. The literature search included published articles from 1993 to November 1998 that reported results from both prospective and retrospective studies with more than 10 subjects. Patients with chronic coronary artery disease and LV dysfunction who were potential candidates for revascularization were included.

This analysis reported similar findings regarding the comparison of PET and SPECT in their accuracy for assessing viable myocardium. Compared to FDG SPECT, PET had a comparable sensitivity and a higher specificity. The assessment summarized findings from a set of (unquoted) prospective/retrospective studies, which reportedly did not have selection bias:

Technique	Sensitivity, %	Specificity, %
Segment-based		
PET	75-95	67-84

Technique	Sensitivity, %	Specificity, %
Thallium-201 SPECT or planar	75-93	31-56
Patient-based		
PET (one study only)	82	88
Thallium-201 SPECT or planar	65-100	55-73

Finally, the assessment found some evidence of the ability of PET to predict outcomes post-revascularization; however, the report concluded a lack of evidence existed to infer the influence of any of the functional diagnostic imaging methods on patient management.

International Network of Agencies for Health Technology Assessment (November 1999)

The International Network of Agencies for Health Technology Assessment (INHATA) published a technology assessment entitled *Positron Emission Tomography: Experience with PET and Synthesis of the Evidence* in response to global interest in the clinical potential of PET for a variety of indications in neuropsychiatry, oncology, and cardiology. This assessment included a summary of 11 different technology assessments that concluded "comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly thallium-201 SPECT." However, like other technology assessments, they concluded that studies comparing PET to other functional imaging modalities including SPECT, dobutamine echocardiography, and MRI were few and methodologically flawed.

AHRQ Expedited Review of the Literature

AHRQ submitted a brief report in October 2001 in response to CMS's July 20, 2001 request for an expedited review of the literature. Their assessment of the literature summarized the three TAs discussed above. In reviewing these TAs, AHRQ concluded, "there is consensus that the specificity of PET is better than SPECT" and "the only reason to prefer SPECT would be based on availability of PET scanners."

Medical Literature

CMS extended their review of evidence for this use of PET to include published articles in the years not covered by any of the technology assessments. This included published articles in PubMed from 1999, 2000, and 2001. The literature review was guided by the methodology described in the Alberta Heritage Foundation for Medical Research's technology assessment (described above). The intention of their TA was to compare the effectiveness of PET in detecting viable myocardium compared to SPECT. This was more in line with the goal of CMS compared to using the methodology described in the Australian Department of Health and Aged Care, which was aimed at assessing the added value of PET after an inconclusive SPECT. All searches were limited to articles published in English and those that contained both "myocardial" and "revascularization." In addition, the literature review was limited to articles that contained medical subject headings (MeSH) terms of "PET" or "positron emission tomography." The review of recently published articles yielded a total of 116 references. Each of the abstracts for these references were reviewed, and based upon this analysis, 23 full articles were reviewed for their appropriateness. Of those 23 articles, only one was appropriate for use, given the evaluation question, and the findings of this article are summarized below.

Siebelink (2001) performed a direct head-to-head comparison of SPECT and PET (also see details in Evidence Table in Appendix). 103 patients (54 randomized to receive SPECT and 49 to PET) were non-consecutively recruited among those patients referred for routine diagnostic coronary angiography (e.g., for angina, myocardial ischemia, arrhythmias, heart failure) and in whom a revascularization procedure was considered. Masking was achieved by using a uniform polar map that did not allow clinicians to distinguish between PET and SPECT imaging.

There was adequate matching of both baseline characteristics and intended treatments (PTCA vs. CABG vs. drug therapy) among both groups, and the follow-up periods were similar (mean 26+/-1 months for PET and 29+/-1 months for SPECT). Cardiac event-free survival was the outcome, and Kaplan-Meier analysis did not show any significant difference between the groups. Overall the study makes a reasonable argument for the equivalence of the methods, under these study conditions. One minor concern is that the study refers only to viable myocardium and does not differentiate between ischemic and non-ischemic tissue.

Position Paper

The American College of Cardiology (ACC) and the American Society of Nuclear Cardiology (ASNC)

On October 2, 2001, CMS received a joint position paper from the American College of Cardiology (ACC) and the American Society of Nuclear Cardiology (ASNC) on FDG PET imaging in the assessment of myocardial viability. The most recent version of the Radionuclide Imaging Guidelines (1995), a publication of the ACC and ASNC, gave FDG PET imaging a Class 1 recommendation for the assessment of myocardial viability in patients with left ventricular dysfunction in planning revascularization. They also stated that "PET FDG imaging is widely accepted by the cardiology community as the gold standard for myocardial viability." 26 articles were reviewed since the 1995 Guidelines that further support their position of the superiority of FDG PET as a functional imaging method for the detection of viable myocardial tissue. A review of these articles found that FDG PET imaging predicted 1) post-revascularization improvement of left ventricular dysfunction and ejection fraction in patients with left ventricular dysfunction; and 2) whether heart failure symptoms and patient survival would improve following revascularization. They also concluded that FDG PET imaging favorably impacts patient management. They urge CMS to cover FDG PET as a primary method and also after an inconclusive or discordant SPECT for assessing myocardial viability.

Analysis of the Evidence

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. § 1869(f)(1)(B). In order to be covered by Medicare an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

Given the variety of items and services that may be covered under the Medicare program and the medical needs of our beneficiaries, the most common method of determining whether the expenses related to items and services are "reasonable and necessary" is to conduct a fact-specific inquiry on a claim-by-claim basis. In deciding claims on this basis, the beneficiary bears the burden of proving entitlement. 42 C.F.R. § 424.5(a)(6) ("The provider, supplier, or beneficiary, as appropriate, must furnish sufficient information to determine whether payment is due and the amount of payment. ") On some occasions, however, the medical and scientific evidence is sufficiently compelling that the agency is able to make a national determination as to whether or not the expenses related to a particular item or service are "reasonable and necessary" for a particular population of beneficiaries with the same salient characteristics. Because NCDs are binding on Medicare contractors and administrative law judges, they often serve to obviate the need for expensive and time-consuming claim-by-claim analysis.

As previously mentioned in this decision memorandum, the use of PET as a primary or initial diagnostic study for determining myocardial viability falls within the benefit category of § 1861(s)(3) diagnostic services. In addition, no statutory provision specifically precludes payment. Finally, we have fully examined the medical and scientific evidence submitted with the request for a national coverage decision, and we have determined that the record currently is sufficient for the agency to make a national determination that the item or service is reasonable and necessary for a particular group of beneficiaries described below.

This memo specifically compares two techniques SPECT and FDG PET. This analysis will focus first on the three technology assessments along with AHRQ's summary assessment, then address the new literature available, and, finally, the position statements provided.

There were three technology assessments reviewed: the Australian Department of Health and Aged Care (August 2000), Alberta Heritage Foundation for Medical Research (October 1999), and the International Network of Agencies for Health Technology Assessment (November 1999). These assessments varied in methodology, search criteria, and included questions not currently under review by this agency. However, they all had commonality in comparing SPECT to FDG PET in some meaningful way.

- The Australian Department of Health and Aged Care concluded that PET had a higher specificity compared to SPECT. In patients with differing test results, PET was a better predictor of myocardial recovery compared to SPECT.
- The Alberta Heritage Foundation for Medical Research reported similar findings as above regarding the comparison of PET and SPECT in their accuracy for assessing viable myocardium. Compared to FDG SPECT, PET had a comparable sensitivity and a higher specificity. The assessment did find some evidence of the ability of PET to predict outcomes post- revascularization; however, the report concluded that a lack of evidence existed to infer the influence of any of the functional diagnostic imaging methods on patient management.
- The International Network of Agencies for Health Technology Assessment (INHATA) assessment concluded "comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly thallium-201 SPECT."

ARHQ was aware that all the assessments reviewed raised questions about the degree of discordant test results, the incremental value of these various forms of testing, and the ultimate quality and adequacy of the studies. Based on their review, they concluded, "there is consensus that the specificity of PET is better than SPECT" and "the only reason to prefer SPECT would be based on availability of PET scanners."

Upon review of the updated literature, the only seemingly pertinent article is by Siebelink. It performed a direct head-to-head comparison of SPECT and FDG PET. Although the study has limitations with respect to outcome benefit and patient selection (ischemic and non-ischemic patient enrollment), the study makes an overall reasonable argument for the equivalence of these two methods. Again, it is important to emphasize that the objective of this evaluation is to simply compare FDG PET to SPECT (an already covered method of assessing myocardial viability). In this regard Siebelink demonstrates equivalence of these two methods.

Finally, on October 2, 2001, CMS received a joint position paper from the American College of Cardiology (ACC) and the American Society of Nuclear Cardiology (ASNC) on FDG PET imaging for the assessment of myocardial viability. CMS recognizes various levels amidst the hierarchy of evidence, and the joint Position Statement reflects data which are beyond anecdotal. They developed a Class 1 recommendation for using FDG PET in the assessment of myocardial viability for patients with left ventricular dysfunction in planning revascularization. Further, they reported (from 26 articles) superiority of FDG PET as a functional imaging method for the detection of viable myocardial tissue, with regard to post-revascularization improvement of left ventricular dysfunction and ejection fraction in patients with prior left ventricular dysfunction and heart failure.

The above evidence builds a strong case for the equivalence of FDG PET as a stand-alone method in the assessment of myocardial viability, relative to existing covered technologies. However, medicine and cardiology, in particular, are rapidly advancing fields. Each patient is unique and presents a different set of variables to the clinician. These variables must be processed and a management plan arrived upon which is best for the patient, the treating physician, and the resources available to them. Heart disease remains the number one cause of death in the United States, and for this reason, medicine continues to search for increasingly better ways to assess the heart and its functional capacity. In the case of assessing myocardial viability, using either FDG PET or SPECT has good diagnostic clinical value. Also, PET may add information following and inconclusive SPECT. However the use of SPECT, following PET, would not be reasonable and necessary because its relatively lower presumed specificity when compared to PET would not improve assessment of myocardial viability.

Decision

CMS intends to revise the NCD at CIM 50-36 to state that (1) both SPECT or FDG PET are reasonable and necessary as a primary or initial diagnostic study for determining myocardial viability prior to revascularization; (2) PET continues to be reasonable and necessary following an inconclusive SPECT; (3) the greater specificity of PET makes using SPECT following an inconclusive PET of no added value and thus not reasonable and necessary.

Appendices

Evidence Table

Author/Year	Intervention	Design	Groups for Comparison	Sampling Criteria	
				Inclusion	Exclusion
Siebelink (2001)	PET (13N + FDG in combination) vs. SPECT in terms of patient management and outcomes.	Random., masked trial in which uniform polar map did not allow clinicians to distinguish between PET and SPECT imaging	SPECT (n=54) vs. PET (n=49)	(1) Pts. Referred for coronary angiography in whom revascularization was considered; (2) Wall motion abnormalities in an area supplied by a stenosed (>50%) vessel for which additional information needed on myocardial viability	(1) <20 & >80; (2) Unstable angina; (3) Acute MI within 4 weeks
F/U time	Results	Limitations (attrition, etc.)	Comment		

Author/Year	Intervention	Design	Groups for Comparison	Sampling Criteria	
				Inclusion	Exclusion
Mean 26 +/- 1 months for PET group vs. 29 +/- 1 months for SPECT group (median 28 vs. 29)	Kaplan-Meier analysis without significant difference in cardiac-event free survival	No data on functional status of patients were obtained during follow-up period	(1) 8 drop-outs described and appear to be well-accounted for; (2) Imaging with both ¹³ N and FDG PET labels does not discriminate between ischemic and non-ischemic, but viable, myocardium; (3) Overall, study makes a reasonable argument for the equivalence of PET and SPECT for guiding patient management, particularly strengthened by proper masking and an adequate sample size		

1 American Heart Association, 2001

2 Ibid.

3 <http://www.cadreversal.com/Myocardial%20Viability/myocardial%20viability.html>

4 Tatoulis, 2000

5 <http://www.fda.gov/OHRMS/DOCKETS/98fr/031000a.txt>

6 Soufer, 1995

7 Maddahi, 1994; Beanlands, 1997

[Back to Top](#)